REMARKS

Applicant requests reconsideration of the application in view of the foregoing amendments and the discussion that follows. The status of the claims as of this amendment is as follows: Claims 1-6 and 37-46 are pending. Claims 7, 8, and 10-24 were previously withdrawn and canceled and Claims 9 and 25-36 were previously canceled. Applicant reserves the right to file divisional applications to the separately patentable subject matter thereof. Claims 1, 44 and 46 have been amended herein.

Applicant wishes to thank the Examiner for the courtesy of a telephonic clarification of the language of the Office Action on November 9, 2005. The Examiner indicated that Applicant should read the Office Action at pages 5-8 by ignoring lined-through language as not part of the Office Action since it was not intended to be present and by treating underlined language as part of the Office Action with no special emphasis implied by the underlining.

The Amendments

The specification was amended in several paragraphs to clarify the relationship between the substrate attached to a surface or support and the detectable product attached to the substrate by a cleavable linker where cleavage of the cleavable linker releases detectable product from the support. Support for these amendments is in the specification, for example, the paragraph bridging pages 36-37 and Fig. 5. Referring to Fig. 5, by way of illustration and not limitation, it is clear that substrate A-B-D, attached to a support represented by a bead in the figure, is cleaved by singlet oxygen to release detectable product B-D from the support.

The paragraph bridging pages 3 and 4 was also amended to recite that one of the receptors of the sandwich has a label and the other receptor of the sandwich has multiple copies of a substrate associated with it. Support therefor is in the specification, for example, Fig. 5.

The paragraph on page 4, lines 20-30, was also amended to recite that the sensitivity of the assay will therefore depend strongly on efficiency of the separation of the free detectable product and detectable product to which the substrate is bound. Support therefor is in the specification, for example, Fig. 5.

The paragraph on page 5, lines 1-14, was also amended to refer to binding sites to make the language of the paragraph consistent. Support therefor is in the specification, for example, the original paragraph on page 5, lines 1-14.

The paragraph on page 9, lines 5-22, was also amended to recite that the receptors are those of the sandwich of the sandwich binding assay. Support therefor is in the specification, for example, the original paragraph on page 9, lines 5-22.

The paragraph on page 38, lines 15-25, was amended to correct a typographical error.

Claim 1 was amended to recite that the substrate comprises a detectable product linked to the substrate through a reactive oxygen cleavable linker. Support therefor is in the specification, for example, the paragraph bridging pages 36-37 and Fig. 5. Claim 1 was also amended to recite "separating the released detectable product from the substrate bound to the support. Support therefor is in the specification, for example, original Claim 1. Claim 1 was also amended to provide a recitation of indirect binding. Support therefor is in the specification, for example, page 54, lines 8-10.

Claim 44 was amended to recite that the substrate comprises digoxigenin-linked biotin linked to the substrate through a reactive oxygen cleavable linker. Support therefor is in the specification, for example, the paragraph bridging pages 36-37 and Fig. 5. Claim 44 was also amended to recite digoxigenin-linked biotin in place of detectable product to provide internal consistency in the language of Claim 44. Support therefor is in the specification, for example, original Claim 44.

Claim 46 was amended to provide proper reference back to Claim 44, from which Claim 46 depends.

Drawings

Applicant acknowledges the indication in the Office Action that the replacement sheets for Figures 9, 10A and 10B submitted in an Amendment under 37 C.F.R. 1.116 mailed on May 24, 2005, were accepted.

Objection to the Specification

Applicant submits that the foregoing amendments to the specification on pages 4 and 5 obviate the objections with regard to pages 4 and 5 raised in the Office Action.

The Office Action further asserts that the mechanism underlying the recited conditional causal relationship on page 6, lines 2-4, is indefinite. Applicant respectfully traverses this objection. The language referred to indicates that, if the amine (identified in the previous sentence as a specific binding reagent that comprises an amine) is attached to a label, reaction with the oxidation product not only releases the product from the support or polymer but also binds the product to the label. One skilled in the art would recognize this language as sufficiently definite. The specific binding reagent may be represented as Label-SB-NH_2 (where SB refers to specific binder). As explained earlier in the specification, the label generates an oxidant that cleaves the linker linking the detectable product (DP) to the substrate and releases DP. As explained earlier in the paragraph, the oxidative cleavage generates an active moiety such as an ester (DP-CO-ester), which is reactive with an amine functionality. Thus, Label-SB-NH_2 reacts with DP-CO-ester to yield Label-SB-NH-CO-DP. Accordingly, not only is detectable product released by the specific binding reagent, the released detectable product also becomes bound to the label by an amide linkage.

The Office Action asserts that the mechanism underlying the recited conditional causal relationship on page 6, lines 4-5, is indefinite. Applicant respectfully traverses this objection. The language referred to indicates that, if the amine is not attached to a label, it can react with the product to produce a new group which can serve as a ligand. One skilled in the art would recognize this language as sufficiently definite. The specific binding reagent may be represented as SB-NH_2 (where SB refers to specific binder). As explained earlier in the specification, the label generates an oxidant that cleaves the linker linking the detectable product (DP) to the substrate and releases DP. As explained earlier in the paragraph, the oxidative cleavage generates an active moiety such as an ester (DP-CO-ester), which is reactive with an amine functionality. Thus, SB-NH_2 reacts with DP-CO-ester to yield SB-NH-CO-DP. As indicated, this product can serve as a ligand (defined in the specification at page 14, lines 18-19), which refers to any organic compound for which a receptor naturally exists or can be prepared.

Accordingly, a receptor with a label may be contacted with the aforementioned ligand to bind to the ligand and provide a label to be detected.

Rejection under 35 U.S.C. 112

Claims 1-6 and 37-46 were rejected under the second paragraph of the above code section as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant submits that the above amendments to the claims obviate these grounds of rejection.

Rejection under 35 U.S.C. 102

Claims 1, 2 and 4-6 were rejected under paragraph (e) of the above code section as being anticipated by Singh, *et al.* (U.S. Patent No. 6,770,439) (Singh).

Singh does not disclose or suggest the method of Claim 1. Among others, there is no disclosure or suggestion in Singh of a method as recited wherein the step of detecting the released detectable product comprises the steps of (a) separating the released detectable product from the substrate bound to the support; (b) adding to the separated released detectable product a third specific binding pair member capable of binding directly to the released detectable product or capable of binding specifically to a specific binding pair member or to a complex of two or more sbp members which is capable of binding to the detectable product; (c) allowing the third specific binding pair member to bind to the released detectable product; and (d) detecting the bound third specific binding pair member.

The Office Action argues that Singh teaches the step of detecting comprising the steps of: separating the released detectable product substrate from the detectable substrate associated with the support (the Office Action refers to col. 36, lines 19-21, of the reference as reciting "the subject heterogeneous assays require that the unbound labeled reagent be separable from the bound labeled reagent"), adding to the separated released detectable product a third specific binding pair member capable of binding directly to the released detectable product, allowing the third specific binding pair member to bind, and detecting the bound third specific binding pair member (the Office

Action refers to col. 40, lines 25-41, of the reference as reciting "e-tags may be reacted with detectable labels" "detectable label may be part of the reagent cleaving the cleavable bond."

There is no disclosure or suggestion in the passages relied on in the Office Action of the addition of a third specific binding pair member capable of binding directly to the released detectable product or of allowing a third specific binding pair member to bind to the released detectable product and detecting the third specific binding pair member. At column 40, lines 34-46, Singh not only does not mention or suggest a third specific binding pair member, the patentee teaches away from such an approach by discussing chemically reactive functionalities for binding to the cleaved e-tags. Singh states that, where detectable labels are not present on the e-tags, the e-tags may be reacted with detectable labels. In some instances the detectable label may be part of the reagent cleaving the cleavable bond, e.g., a disulfide with a thiol. Where there is a plurality of different functionalities on different binding members for reaction with the label, the different labels will have functionalities that react with one of the functionalities. The different labels may be added together or individually in a sequential manner. For example, where the functionalities involve thiols, carboxyl groups, aldehydes and olefins, the labels could have activated olefins, alcohols, amines and thiol groups, respectively.

With regard to the rejection of Claims 2 and 4-6, respectively, at the very least these claims are patentable over the reference because of their respective dependencies from Claim 1, which is patentable over the reference as discussed above.

Rejection under 35 U.S.C. 103

Claims 3 and 37-43 were rejected under paragraph (a) of the above code section as being unpatentable over Singh in view of Oh and Steinberg (U.S. Patent No. 5,851,77) (Oh).

The Office Action refers initially to certain passages of Singh. As recognized in the Office Action, these passages do not teach digoxigenin linked biotin. At col. 29, lines 5-15, Singh, in discussing capture ligands, states that other reagents that are useful include a ligand-modified nucleotide and its receptor. Ligands and receptors include

biotin and strept/avidin, ligand and antiligand, e.g., digoxin or derivative thereof and antidigoxin, etc. By having a ligand conjugated to the oligonucleotide, continues the patentee, one can sequester the eTag conjugated oligonucleotide probe and its target with the receptor, remove unhybridized eTag reporter conjugated oligonucleotide and then release the bound eTag reporters or bind an oppositely charged receptor, so that the ligand-receptor complex with the eTag reporter migrates in the opposite direction.

Figs. 3A and 3B support the fact that Singh does not teach anything more than using biotin or avidin or digoxin or anti-digoxin as a ligand or receptor linked to an oligonucleotide. Fig. 3B shows biotin linked to an e-Tag. There is no disclosure of digoxigenin linked biotin.

The Office Action asserts, however, that Oh teaches the use of digoxigenin linked biotin, referring to Oh, col. 16, lines 30-38, in support thereof. Oh teaches tridentate conjugates involving small molecules, which are linked to an analyte as the second member of the tridentate. For example, for theophylline Oh mentions biotin-theophylline-DNP or biotin-theophylline-biotin. At the cited passage, Oh also indicates that other analyte drugs that may be assayed include digoxin, etc. Accordingly, the skilled person would understand that, if the analyte is digoxin, then the tridentate would have two small molecules linked to digoxin such as, for example, biotin-digoxin-biotin. The tridentates are used in competition assays where the analyte member of the tridentate competes with the analyte of the sample for binding to a specific binding partner for the analyte (col. 15, lines 26-40).

Oh's disclosure has no relevance to the teaching of Singh and, thus, one skilled in the art would not be motivated to use the tridentate conjugate of Oh in the method of Singh. The Office Action contends that the skilled artisan would be motivated to make such a combination because Oh discovered that tridentate conjugates do not require "expensive isolation and characterization procedures of prior art reagents" and exhibit "longer shelf life" than prior art counterparts. However, as explained above, the reagents taught by Oh are tridentates that have two small molecules linked to an analyte. Such a reagent is not digoxigenin linked biotin and is not suggestive of digoxigenin linked biotin. Therefore, the motivation proffered by the Office Action is not relevant to the presently claimed reagent. The design of such a reagent is only taught in

Applicant's specification.

Furthermore, even if the skilled artisan were motivated to make the combination set forth in the Office Action, one still would not be in possession of the invention of Claims 3 and 37-43. There is no recognition of using digoxigenin linked biotin as part of a substrate in an assay where cleavage of an oxidant cleavable linker releases digoxigenin linked biotin as a detectable product. At most, the combined teaching of Singh and Oh would employ a tridentate conjugate as a capture ligand as taught by Singh. Such a tridentate conjugate, involving two small molecules linked to analyte, and its use are completely different from the detectable product of the above claims.

The Office Action argues that Applicant's previous argument was carefully considered but was not persuasive because Oh & Sternberg provide a general teaching of a reagent for use in "analyte assays" (see Title). The Office Action asserts further that, insofar as Applicants' invention, as currently claimed, is also a general disclosure of an "analyte assay", the teachings of Oh & Sternberg appear highly relevant.

First, the motivation necessary is that for combining the teachings of two or more references, not for the combining of the teaching of a reference with the teaching of a specification of an application under examination. Furthermore, as explained above, the motivation to combine Singh and Oh is not persuasive. Second, the combined teaching of the references does not result in the reagent of the present claims, namely, dioxigenin linked biotin. Oh teaches a tridentate reagent having two small molecules linked to an analyte of an assay. To employ such a reagent in Singh does not result in the presently claimed invention.

Claims 44-46 were rejected under paragraph (a) of the above code section as being unpatentable over Singh in view of Oh. For reasons similar to those discussed above with regard to the rejection of Claims 3 and 37-43 under the above code section, Claims 44-46 are patentable over the combination of teachings of Singh and Oh. Again, there is no recognition of using digoxigenin linked biotin as part of a substrate in an assay where cleavage of an oxidant cleavable linker releases digoxigenin linked biotin as a detectable product. At most, the combined teaching of Singh and Oh would employ a tridentate conjugate as a capture ligand as taught by Singh. Such a tridentate conjugate and its use are completely different from the digoxigenin linked biotin of the

above claims.

Conclusion

Applicant has demonstrated that Claims 1-6 and 37-46 satisfy the requirements of 35 U.S.C. 112, 102 and 103. Furthermore, the specification is free of informalities. Allowance of the above-identified patent application, it is submitted, is in order.

Respectfully submitted,

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